


Cigarette Smoke and Ozone-Induced Epithelial Perturbation In Vivo and In Vitro*

The Role of Glutathione

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Increased airspace epithelial permeability (EP) occurs in cigarette smokers and in normal subjects exposed to ozone (O$_3$), a component of cigarette smoke (CS). Since both O$_3$ and CS have oxidant potential, we hypothesized that the mechanism of increased EP to both CS and O$_3$ results from oxidant stress and perturbation of the airspace epithelium. Human and animal studies by our group and others have previously shown profound changes in the lung antioxidant-reduced glutathione (GSH) following CS exposure. We tested the hypothesis that oxidant stress causing changes in GSH was the underlying mechanism of the increased EP in smokers following O$_3$ exposure in vivo and in an in vitro model of EP.

EP, as measured by the clearance of inhaled technetium 99m-diethylenetriamine penta-acetic acid, was increased in chronic smokers compared to nonsmokers, with a further significant increase in acute smokers (p<0.01). No such effect was noted in healthy subjects 1 or 6 h after exposure to O$_3$ (200 and 400 parts per billion, during intermittent exercise for 1 h). The twofold increase in GSH, which occurred in epithelial lining fluid in chronic smokers, was not present in acute smokers. Evidence of oxidant stress, shown by elevated products of lipid peroxidation, and decreased antioxidant capacity in plasma, which correlated with increased O$_2$-release from neutrophils, occurred in smokers, but not after O$_3$ exposure.

In vitro exposure of airspace epithelial cell monolayers to CS and O$_3$ both increased EP to $^{125}$I-bovine serum albumen, which in the case of CS was associated with an initial decreased intracellular GSH, followed by a rebound increase in GSH 12 h after exposure due to increased expression of messenger RNA for gamma-glutamylcysteine synthetase, by a mechanism involving the AP-1 transcriptional factor. Increased EP to both O$_3$ and CS in vitro was also associated with profound changes in the cytoskeleton. These data explain the mechanism of CS-induced EP and the increase in GSH in chronic smokers.

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